Remarks

Claims 1-7, 9-25 and 27-54 are pending in the application. Claims 1-7, 9-19, 24, 25, 27-33 and 48-54 are allowed. Claims 20-23 and 34-47 stand rejected. Claim 26 is objected to. Claims 20-23 and 34-41 are amended herein. Reconsideration is respectfully requested in view of the following comments.

Response to Objection to Claim 26 for Improper Format

The Examiner objected to claim 26 as being in improper format, for allegedly not further limiting claim 24, from which claim 26 depends. Applicants respectfully submit that claim 26 has previously been cancelled by way of the Preliminary Amendment submitted on July 29, 2003. However, Applicants' attorney inadvertently listed claim 26 in the claim listing submitted with the amendment on July 14, 2005. Applicants respectfully submit that this was merely a clerical error, and have properly indicated claim 26 as "cancelled" in the claim listing submitted herein.

Response to Objection to the Amendment for Improper Claim Format

The Examiner has objected to the amendment submitted on July 14, 2005, as being in improper format. Specifically, the Examiner asserted that in accordance with 37 C.F.R. § 1.173, the claims listed in an amendment filed during a reissue examination must be relative to the original patent claims. Applicants have made this correction, and accordingly, the claim listing set forth herein properly reflects the claim amendments relative to the original patent claims.

Response to Rejection under 35 U.S.C. § 112, first paragraph

Applicants note that the Examiner has indicated that the specification is enabling for "treating inflammation."

Claims 20-23 and 34-47 were rejected pursuant to 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Applicants respectfully disagree, particularly in view of the claim amendments set forth herein, and submit that claims 20-23 and 34-47 are enabled under 35 U.S.C. § 112, 1st paragraph, for the reasons set forth below.

As a preliminary matter, Applicants have amended claims 20-23 and 34-41 to more specifically point out that the claimed methods of treating cyclooxygenase-

mediated disorders, inflammation, inflammation-mediated disorders, angiogenesis-mediated disorders, neoplasias, and neoplasias that express cyclooxygenase, encompass those conditions and disorders in which cyclooxygenase-2 ("COX-2") plays a role. Specifically, the claims have been amended to recite that the method of treatment is directed to those conditions and disorders that are mediated by COX-2. Support for these amendments can be found throughout the specification, and in particular, in column 11, from 51 through line 56.

As asserted previously, Applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. 112, unless there is a reason to doubt the objective truth of the specification. See, *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The initial burden of establishing a basis for denying patentability to a claimed invention rests upon the examiner. See, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). Applicants respectfully submit that the Examiner has not met this burden.

The test of enablement is not whether *any* experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)).

The Examiner alleges that the "specification does not enable any person skilled in the art to which it pertains...to use the invention commensurate in scope with these claims." The Examiner provides an analysis of some of the *Wands* factors (*In re Wands*, 8 USPQ2d 1400). However, it is Applicants' view that the Examiner's analysis of the *Wands* factors does not meet the burden to establish that the amended claims are not enabled. The *Wands* factors analyzed by the Examiner are addressed below.

Predictability in the art and the quantity of experimentation needed.

The Examiner states that the pharmaceutical art is unpredictable, and that "each embodiment of the invention is required to be individually assessed for physiological activity." The Examiner goes on to cite Golub *et al.* "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring" as evidence of unpredictability in the art of cancer therapy. The Examiner states that "[T]he various types of cancers have different causative agents, involve different cellular mechanisms, and consequently differ in treatment protocol" (emphasis added).

Applicants respectfully submit that the amended claims cannot be properly characterized by the Examiner's application of Golub. In particular, the amended claims clearly indicate that the claimed methods are directed to treating conditions or diseases that are mediated by COX-2. As such, the claims are drawn to those cells that involve a particular cellular mechanism, namely, COX-2 activity. Therefore, regardless of the causative agent of a cancer, for example, cancer cells that involve COX-2 activity are all amenable to treatment according to the presently-claimed invention. Further still, because the claimed methods are drawn to numerous conditions and disorders which all comprise the common mechanism of COX-2 activity, any cells involved in any such conditions or disorders are equally amenable to treatment according to the present invention.

The Examiner's analysis of the state of the art at the time of the Application neglects to mention the considerable amount of literature disclosing therapeutic potential of cyclooxygenase inhibitors, particularly COX-2 inhibitors, in treating tumors that express cyclooxygenase. See, for example, Gupta *et al.* (PMID:10579801, abstracting *Prostate*; 2000, 41(1); page 73-78) which states, "Aberrant or increased expression of cyclooxygenase (COX)-2 has been implicated in the pathogenesis of many diseases including carcinogenesis. COX-2 has been shown to be over-expressed in some human cancers." Gupta's analysis of data for COX-2 expression in prostate tissue showed utility of COX-2 inhibitors "for prevention or therapy of prostate cancer in humans." See also, Yip-Schneider *et al.* (PMID:10657949 abstracting *Carcinogenesis*, 2000, 21(12), page 139-46) which states, "COX-2 expression is up-regulated in several types of human cancers and has been directly linked to carcinogenesis." Yip-Schneider evaluated the

role of COX-2 in pancreatic cancer and concluded that "COX-2 may play an important role in pancreatic tumorigenesis and therefore be a promising chemotherapeutic target for the treatment of pancreatic cancer." See also Ochaia *et al.* (PMID: 10665651, abstracting *Jpn. J. Cancer Res.*, 1999, 90(12), page 1338-43). Based on known COX-2 expression in various human cancers, Ochaia investigated COX-2 expression in non-small cell lung cancers (NSCLC) and concluded that "COX-2 may be associated with carcinogenesis of NSCLC, and that it may be a target for the treatment of NSCLC." See also Komhoff *et al.* (PMID 10880372, abstracting *Am. J. Pathol.*, 2000, 157(1), page 29-35). Komhoff states that, "Studies in human and animal models have shown that COX-2 is up-regulated in several epithelial carcinomas including colon, breast, and lung." Komhoff investigated COX-2 involvement in human bladder cancer and demonstrated "elevated expression of COX-2 in a high percentage of high-grade bladder carcinomas, suggesting a possible role of COX-2 in the progression of bladder urothelial carcinoma and supporting its potential as a therapeutic target in human bladder carcinoma."

The references above (PubMed Abstracts attached hereto as Exhibit 1) demonstrate that the state of the art includes recognition that tumors expressing a cyclooxygenase respond to treatment with a COX-2 inhibitor. The references further show that determination of cancers that express COX-2 constituted experimentation that did not rise above a level that was routine in the art.

By way of example, Applicants respectfully submit that celecoxib, a COX-2-specific inhibitor, is well known in the art for the treatment of inflammation and inflammation-*related* disorders. It is well-established that the effect of celecoxib is mediated by the inhibition of COX-2. Additionally, Applicants respectfully point out that the disclosure of U.S. Patent No. 5,972,986, which was incorporated by reference in its entirety into the present application, demonstrates the successful treatment of a cancerous tumor using a COX-2-specific inhibitor. Specifically, column 12 in patent 5,972,986 describes the treatment and shrinkage of a tumor in a mammal by treatment of the tumor with a COX-2-specific inhibitor. Therefore, the treatment of COX-2-mediated conditions and diseases with COX-2-specific inhibitors was well-established at the time of filing of the present application, and such treatment is well within the ability of the ordinary skilled artisan.

The above-cited references, taken in conjunction with the disclosure of the present invention, correlate the inhibition of COX-2 activity and the in vitro treatment of cancer cells with the presently-claimed treatment of cancer. Experimental Example 24 in the present application discloses the efficacy of compounds of the invention for inhibition of colon cancer cells, as well as for direct inhibition of cyclooxygenase activity of COX-2. It follows, based on the level of skill in the art at the time of filing of the present invention, that the skilled artisan, when armed with the disclosure of the present invention, would be able to practice the claimed invention. For example, the skilled artisan would know how to assay a compound of the invention, how to identify inhibition of COX-2 enzymatic activity using a compound or method of the invention, how to identify inhibition of a cancer cell using a compound or method of the invention, and, accordingly, how to identify successful treatment of a patient using a compound or method of the invention, based on the inhibition of COX-2. It would not require undue experimentation to determine whether a tumor, for example, stopped growing or shrunk upon treatment according to the present invention. Similarly, it would not be undue experimentation to administer a compound according to the present invention to a patient suffering from prostaglandin-mediated inflammation and subsequently, to determine whether inflammation has subsided in the patient. Applicants respectfully submit that these techniques are well within the range of the ordinary skilled artisan.

Moreover, the compounds and methods of the present invention are applicable to other cell types, as well as other conditions and diseases, provided that such cells, conditions and diseases are mediated by COX-2. That is, the invention is also adequately enabled for treatment of any cell with any disease or condition that is related to COX-2 activity in the cell. As further proof that the claimed invention was adequately enabled at the time of filing, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by inventor D.V. Ramana Reddy (the "Declaration"). This declaration presents post-filing data that demonstrates a further reduction to practice of the invention claimed and set forth in the as-filed application.

For example, paragraphs 4 and 5 of the Declaration describe the inhibitory effect of compounds of the invention on various human colon cancer cell lines, and paragraph 11 further demonstrates the inhibitory effect of compounds of the invention on COX-2

enzyme *in vitro*. Paragraph 6 of the Declaration illustrates the inhibitory effect of compounds of the invention on cancer cells from various sources, including colon, breast, brain, and prostate. The data in the Declaration shows the COX-2 specific and superior effect of compounds of the invention when examined alongside celecoxib, which is another COX-2 inhibitor.

Significantly, the data in the Declaration also demonstrate that the compounds and methods of the invention are widely applicable to any cell in which COX-2, and the activity of COX-2, plays a role. This is because the compounds of the invention specifically inhibit the activity of COX-2.

Furthermore, the Declaration demonstrates the COX-2 inhibitory effect of compounds of the invention on non-cancer cells. Paragraphs 9 and 10 demonstrate the neuro-protective effect of compounds of the invention via COX-2 inhibition in neuronal cells. Compounds of the invention also prevent oxidative stress-induced programmed neuronal cell death, by way of COX-2 inhibition in neuronal cells (see paragraph 10 in the Declaration).

The data set forth in the Declaration corroborates the disclosure set forth in the as-filed application, as well as the concepts presented in the reference abstracts attached herewith. That is, the Declaration provides further proof that the present invention is broadly useful, because the compounds and methods of the invention are useful to treat any disorder or condition, in any cell, when the activity of COX-2 plays a role in the disorder or condition. The Declaration further provides proof that *in vitro* COX-2 inhibition correlates with a whole-cell effect of COX-2 inhibition (eg., cancer cell killing or neuronal cell protection), and further, that both of these findings correlate well with the treatment of conditions or diseases related to COX-2 activity (eg., neoplasia or inflammation). Further still, the Declaration provides support that compounds encompassed by the claims in the present application are equally useful and effective according to the activity and methods of the invention.

As set forth in detail in the present application, as well as in the references cited herein and in the hundreds of references not expressly provided herein, the art is such that the inhibition of COX-2 activity *in vitro* and in whole cells is understood to be well-correlated with treatment of a condition in a patient, wherein the condition is associated

with the expression or level of COX-2 activity. MPEP section 2164.02 states that "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." The Examiner has not provided any such evidence in the office action. To the contrary, the Examiner has conceded that the present invention is in fact enabled for the treatment of inflammation, thereby acknowledging that the inhibition of COX-2 *in vitro* and in whole cells correlates with the treatment of a patient according to the present invention. Therefore, Applicants respectfully submit that the pending claims, including the amended claims, are indeed adequately enabled.

The Examiner states that there are no "working examples" for the treatment of any cyclooxygenase-mediated disorder, neoplasia, neoplasia that expresses a cyclooxygenase, inflammation-mediated disorder, or angiogenesis-mediated disorder. Applciants respectfully disagree with this basis for the Examiner's citation of a lack of enablement, particularly in view of the amended claims. The claims have been amended to recite that the methods of treatment are directed to those conditions and disorders that are mediated, at least in part, by COX-2. Therefore, the present invention is enabled for any COX-2-mediated disorder, neoplasia, neoplasia that expresses a cyclooxygenase, inflammation-mediated disorder, and angiogenesis-mediated disorder.

The Examiner also states that, "[O]ne of skill in the art would need to determine what diseases would be benefited (treated) by inhibition of cyclooxygenase. . ." Again, Applicants respectfully submit that the practice of the invention does not require that one determine what diseases could be treated. Applicant's patent specification points out numerous cyclooxygenase-mediated disorders including inflammatory disorders such as rheumatoid arthritis and other disorders listed at column 12, line 1-25, cyclooxygenase expressing neoplasias such as those listed at column 12, line 45-55, and angiogenesis-mediated disorders such as those listed from column 12, line 66 to column 13, line 4. Furthermore, the present application incorporates by reference the teaching of US patent 5,972,986 that neoplasias that express a cyclooxygenase may be treated by administering a cyclooxygenase inhibitor.

In *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim would is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for assessing the utility of the claimed compounds are well-known in the art and/or disclosed in the specification and where the compounds to be tested are listed and properly described and enabled, it would not be undue experimentation to screen for compounds which have the disclosed utility where the art typically engages in such experimentation (*e.g.*, treatment of a condition or disease by way of COX-2 inhibition).

Additionally, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays the compounds for the asserted utility (*e.g.*, COX-2 inhibition), it is not undue

experimentation for them to do so. This also applies regardless of the method of measuring the inhibition of COX-2.

Thus, where one skilled in the art would have routinely screened various compounds to determine inhibition of COX-2, following the teachings of the disclosure provided in the specification as filed, such experimentation would not have been undue even if it was complex. Furthermore, where one skilled in the art would have routinely used such compounds to treat of a patient having a disease or condition mediated by COX-2, such experimentation would not have been undue even if it was complex. Armed with the teachings of the instant invention and what was already known in the art, the routineer would not have had to engage in any undue experimentation to practice the invention commensurate with the scope of claims 20-23 and 34-47, and these claims are therefore enabled under 35 U.S.C. § 112, first paragraph.

The nature of the invention.

The Examiner correctly states that the invention as set forth in claims 20-23 and 34-47 is directed to methods of treating cyclooxygenase-mediated disorders, inflammation-mediated disorders, angiogenesis-mediated disorders, neoplasias, and neoplasias that express cyclooxygenase. Applicants respectfully submit that treatment of such disorders and conditions is known in the art, and that the methods of treatment – and methods of monitoring and evaluating such treatment – were well-known in the art at the time of filing of the present application. Therefore, Applicants submit that the nature of the present invention is such that the skilled artisan could practice the present invention without undue experimentation at the time of filing of the present application.

The state of the art.

The Examiner states that the state of the art "involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (*i.e.* what compounds can treat which diseases and by what mechanism). If "screening *in vivo* and *in vitro*" embodies the state of the art, as asserted by the Examiner, then such experimentation would appear to be routine and therefore not undue experimentation.

Applicants respectfully point out that a necessary element of the methods of treatment claimed in claims 20-23 and 34-47 is the mechanism of action, *i.e.*, COX-2 inhibition. The practice of the invention therefore does not require determination of the mechanism whereby the compounds act. The invention encompasses the treatment of conditions and diseases which are mediated, in part, by COX-2. Accordingly, Applicants submit that the mechanism of treatment is clearly defined.

The level of skill in the art.

The Examiner states, on page 4 of the office action, that the level of skill in the art is "seemingly" high. However, on page 6 of the office action, the Examiner confirms that "the level of skill in the art *is* high" (emphasis added). Applicants agree. By acknowledging that the level of skill in the art is high, the Examiner has conceded this *Wands* factor, effectively removing this factor from further consideration.

Summary of *Wands* factors in *In re Wands.*

Analysis of the *Wands* factors, as the factors were weighed by the court in *In re Wands,* shows that the claims presently at issue are enabled under 35 U.S.C. § 112, first paragraph. In *In re Wands*, the court found those claims were enabled, and stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. *In re Wands*, 8 USPQ2d at 1406 (emphasis added).

In the present application, the claims at issue recite a method of treating a cyclooxygenase-mediated disorder (claims 34-36), and a tumor that expresses cyclooxygenase (claim 40), comprising administering a compound that is a member of a defined chemical genus shown experimentally to inhibit COX-2.

The specification provides:

- a defined genus of compounds that selectively inhibit COX-2;
- a working example providing an experimental protocol capable of determining whether a compound inhibits COX-2; and
- a working example providing an experimental protocol for determining whether a compound inhibits tumor cell growth.

Knowledge in the art included:

- knowledge and skill sufficient for determining which tumors express a cyclooxygenase by experimentation that was routine in the art;
- knowledge that tumors expressing a cyclooxygenase are treatable with cyclooxygenase inhibitors; and
- knowledge that disorders involving the activity of COX-2 can be treated using inhibitors of COX-2.

Where the art typically engages in a complex, but routine degree of experimentation, such activity, as a step in practicing the invention, is not undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning employed by the court in *In re Wands*.

Furthermore, it is well-settled that applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require *any* working examples.

Accordingly, Applicants respectfully submit that claims 20-23 and 34-47 are enabled, and request that the rejection of the claims be reconsidered and withdrawn in view of the amendments and arguments set forth above.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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